Citizens' Environmental Coalition

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January 22, 2013

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Research Triangle Park, NC

Sent Via Email: olden.kenneth@epa.gov; vandenberg.john@epa.gov; cowden.john@epa.gov; sams.reeder@epa.gov; cogliano.vincent@epa.gov

Dear Sirs,

Subject: Recommendations regarding US EPA's Toxicological Review of Inorganic Arsenic - Scoping and Planning

Citizens' Environmental Coalition is a statewide environmental coalition working within a larger public interest network of national, state, local and professional environmental and health organizations committed to chemical policy reform. We appreciate EPA's interest in increasing the involvement of public stakeholders in the IRIS Assessment process.

Toxicological reviews are an essential part of the nation's public health system. The great sanitary movement in the early 19th century was grounded in the realization that environmental factors had enormous impacts on public health. Reformers took a series of actions to address sanitation, proper waste disposal, separating industrial operations from residences, providing clean water and improved housing. Public health developed initially as a means of improving health by addressing environmental conditions for large numbers of people. Prevention of disease and illness was also found to be more cost-effective than treatment.

Today our so-called public health system is vast, involving many agencies and a diverse array of activities. Unfortunately many of these activities are launched, undertaken and completed without a full discussion of how the activity relates to protecting the public health and preventing disease. This is a shame: first, those conducting a toxicological review should understand that the goal is public health protection; and second, the public needs to perceive the work as related to public health, in order to provide the political support and funding necessary for the program.

What does a Toxicological Review in general need?

These are general recommendations, not specific to arsenic.

- A clearly stated public health goal
- Selection of the best science, using scientists in varied disciplines, epidemiology, toxicology, molecular biologists, researchers, public health professionals and clinicians
- Screening out biased, industry-funded studies
- Choosing expert panels, with appropriate expertise, but no financial conflicts of interest
- A strong government role that ensures that the public interest is protected from the undue influence of those with primarily financial interests.
- Reduction in inequality among stakeholders. Industry is always considered a stakeholder, so government should not facilitate undue industry influence. In fact, industry has wielded extraordinary impacts on public health protection by a strategy of questioning the science and manufacturing uncertainty. "Doubt is our product since it is the best means of competing with the 'body of fact' that exists in the minds of the general public. It is also the means of establishing a controversy." (From a document by a tobacco executive cited in *Doubt Is Their Product*, David Michaels, 2008.) The negative impact of this strategy on public health would be demonstrated to be unacceptable to the public, if the collective effects of just a few notable examples were compiled together in one report, such as lead, asbestos, tobacco.

  Instead, government should make greater provision for public interest input, by providing multiple opportunities for input. Most public interest organizations have no ability to send a full time scientist to days of meetings over the course of many months.
- Comprehensiveness: total exposure estimates, all exposure pathways, all adverse effects, all chemical entities, including metabolites, and all people, including vulnerable or special populations. Vulnerable populations can be vulnerable because of greater exposures, such as workers, or because health statistics show greater mortality and morbidity in the population. Pregnant women and children always need to be considered vulnerable populations.
- Qualitative evaluation by health professionals and those in related fields. Before proceeding to any type of quantitative considerations such as dose response, there should be a comprehensive review of the evidence and preparation of a qualitative evaluation including:

  1) Weight of evidence evaluation of all the potential health impacts
  2) Evaluation of serious versus less serious health effects.
  3) Mode of action information
  4) Relevant morbidity and mortality information, major diseases and killers, geographic pattern of disease and vulnerable populations, i.e., African-Americans, Hispanics, etc., trends over time.

  The qualitative evaluation should capture an overall picture of the toxicity of arsenic, what is well-known, as well as emerging evidence, even if the evidence is insufficient to allow quantification.
- Connection to timely action. Timely action has been emphasized in National Academy reports related to Risk Assessments. The purpose of a Toxicological Review is to inform health- based standards and regulations-- this is the Action related to public health. It should be understood that toxicological reviews are not just about science, but about setting health protective standards. Undue delays spurred by industry demands, not reasonable science, delay public health protection. Industry has used an assortment of strategies to prevent, delay and weaken standards and regulations by attacking the

science, arguing always that the evidence is not adequate, that mechanisms are not known, or that it is impossible to set a dose response level. These efforts has been well documented by the historical record. Dioxin is a recent example of industry efforts that have delayed public health actions for decades.

- Transparency is important to democracy. We recommend a transparent process from the beginning and a comprehensive final report that includes a good summary of the evidence, or lack thereof, presentation of the review process, the conclusions and recommendations for health- based standards.
    - The entire process should be clearly laid out at the beginning.
    - The final report should embody a comprehensive review, but also include a summary of the evidence and a discussion of all health effects by category. Where there is no evidence for a category or limited evidence, like reproductive/developmental, that should be stated.(This is not true of arsenic of course.) Information on health effects that have not been adequately studied is also important to the public. Frank health conditions as well as precursor adverse effects should be covered.
    - Too often reports of assessments identify the selected sensitive endpoint (non-cancer) without presenting the other endpoints considered or why that endpoint was selected. Transparency of the process should be part of the final report.
- Public education. A good summary for the Toxicological Review is a critical piece of information that can be used as a basis for preparation of fact sheets and flyers that inform the public about a particular toxic substance.

Inorganic Arsenic

The Process so far on Inorganic Arsenic

While we definitely appreciate the opportunity to provide input, we found the public stakeholder meetings to be very disappointing. Some brief comments: the planned process was not presented; no comprehensive review of arsenic in presentations--a long list of non-cancer effects was shown, but most of these were not discussed at all; no response at all was provided when panelists were asked about reproductive/developmental effects; focus was primarily on frank health effects, like diabetes, with the next step described as dose response evaluation, not consideration of more sensitive early adverse effects and effect levels; and finally, entirely too much industry involvement on panels.

Inorganic Arsenic

Arsenic has been known to be poisonous for hundreds of years. More recent evidence has only increased the evidence of its toxicity at very low doses. As a known human carcinogen, only a zero dose is without risk from arsenic. Unfortunately, the entire population is exposed to arsenic levels above zero.

While the oral route has been well covered, inhalation and dermal exposure pathways need more attention. The inhalation pathway is particularly important because of arsenic in fossil fuels. It is worth noting that criteria air pollutants have been studied in more depth than toxic air pollutants. However, a considerable body of health literature has accumulated related to particulate matter, especially fine particulate matter. While fine particulate matter is a criteria pollutant, it is not homogeneous, and is known to serve as an especially effective carrier of a variety of very toxic pollutants, including heavy metals, organic chemicals, PAHs and products of incomplete combustion. Fine particulate matter delivers its toxic load directly to the lung and bloodstream and this in many instances will include arsenic.

Carcinogenicity and non-cancer health impacts may be related to arsenic's genotoxic or epigenetic effects, including endocrine disruption. As a consequence, for non-cancer health effects, we need to be looking at very low dose adverse effects for arsenic- close to zero.

The Qualitative Evaluation of inorganic arsenic by health professionals and those in related fields.

This topic included above, as a necessary element for all toxicological reviews, needs additional discussion in the case of arsenic. In the January 8th workshop, several presenters suggested after discussing frank diseases that the next step should be dose response. At the same time presenters failed to discuss a number of sensitive endpoints of particular concern for arsenic:

- Genotoxic & epigenetic effects- multiple effects
- Neurological effects- central nervous system and peripheral
- Reproductive/ developmental- spontaneous abortion, structural birth defects, functional deficits, low birth weight, neurological and hearing loss.
- Endocrine disruption- multiple effects, some connected to genotoxic or epigenetic effects.

Before proceeding to any type of quantitative considerations such as dose response, there should be a comprehensive review of the evidence and preparation of a qualitative evaluation including:

Evaluation of serious versus less serious health effects.
In the case of arsenic we have a large number of quite serious health effects--cardiovascular, neurological, immune system, reproductive/developmental, endocrine disruption, genotoxicity, epigenetic effects, etc. In the 2007 ATSDR toxicological profile, skin was chosen as the non-cancer sensitive endpoint.

Given the extensive arsenic literature we believe it should be possible for scientists to identify many sensitive endpoints, particularly those leading to more severe outcomes and thoroughly discuss them before moving to choose an endpoint based solely on the availability of dose-response information.

A careful qualitative evaluation is what is needed by a number of expert professionals using their judgment about the evidence and whether or not serious health effects should be prioritized over less serious endpoints.

Mode of action information should be considered.
In the case of arsenic we have research findings regarding modes of action. Such information should be used in considering the multiple arsenic effects in humans and animals and whether the modes of action point to the need for more protective standards.

Relevant morbidity and mortality information, major diseases and killers, geographic pattern of disease and vulnerable populations, i.e., African-Americans.
There is a causal link between arsenic and cardiovascular disease and hypertension. Hypertension and cardiovascular disease are major killers and also associated with major morbidity, hospitalizations, high costs, etc. Diabetes is also linked to arsenic exposure. The incidence of diabetes has been increasing over time as well as morbidity and mortality associated with diabetes and its many complications.

African-Americans also have a much higher rate of cardiovascular disease and hypertension than Caucasians, as much as three-fold, including young adults. While it certainly would be useful to understand the possible differences in arsenic exposures, in the absence of such information, the evaluation must consider the need for greater protection for some groups based on health disparities, and certainly when we are talking about a major killer. In the 2001 update on Arsenic in Drinking water, the NAS acknowledged the fact that the metabolism of arsenic varies markedly between individuals and that this should be considered in assessing risks.

Weight of evidence evaluation of all the potential health impacts

The expert professional assessment of all the evidence is essential. It should be acknowledged that arsenic has many serious adverse health outcomes at low doses--cancer, genotoxicity, cardiovascular disease, reproductive/ developmental, immune system and endocrine disruption. In addition there is the strong potential that other health impacts are as yet unknown, because of recent mode of action findings and other studies. A weight of evidence evaluation requires expert professional judgment.

Endocrine disruption

While a great deal of attention has focused on sex hormones, other hormone systems are critical at the cellular level. The glucocorticoid hormone system plays an important role in glucose regulation, as well as carbohydrate, lipid and protein metabolism. It helps regulate immune, circulatory and renal function. Additionally, the glucocorticoid system influences growth (including weight regulation), development, bone metabolism and central nervous system activity.

By implication, disrupting the glucocorticoid system can have profoundly negative impacts on development and health. Dysfunction in the glucocorticoid system has been linked to weight gain/loss, protein wasting, immunosuppression, insulin resistance (which can lead to diabetes), osteoporosis, growth retardation, and hypertension.

Kaltreider *et al.* demonstrate that, at extremely low levels of exposure, levels far too low to identify cell damage or 'traditional' toxicity, arsenic alters hormonal function in the

glucocorticoid system. The metal interferes with glucocortoid signaling necessary to turning on genes involved in tumor suppression and other activities. By preventing these genes from turning on, arsenic may increase the risks of cancer. This new result may require radical strengthening of arsenic exposure standards, because it takes place at levels far beneath current safety thresholds.

Kaltreider, RC, AM. Davis, JP Lariviere, and JW Hamilton 2001. "Arsenic Alters the Function of the Glucocorticoid Receptor as a Transcription Factor." *Environmental Health Perspectives 109:245-251*.

It should be noted that "interference with estrogen, androgen, glucocorticoid or thyroxine receptor function can result in developmental and endocrine toxicities." *Scientific Frontiers in Developmental Toxicology and Risk Assessment*, NRC, Committee on Developmental Toxicology, 2000, p.34.

We have selected several articles of interest below. Given the short time period before the National Academy meets, and that the purpose of this letter is to provide scoping and planning comments, we have not attempted an extensive literature review.

Thank you for your attention.

Sincerely,

Barbara J. Warren RN, MS
Executive Director
Citizens' Environmental Coalition

Attachments

Environ Health Perspect. 2012 June; 120(6): 779–789.
Published online 2012 February 1. doi: 10.1289/ehp.1104597
PMCID: PMC3385443
Review

Role of Environmental Chemicals in Diabetes and Obesity: A National Toxicology Program Workshop Review

Kristina A. Thayer,[1] Jerrold J. Heindel,[2] John R. Bucher,[3] and Michael A. Gallo[4]

Arsenic. The breakout group participants that evaluated this literature concluded that the existing human data were limited to sufficient in support of an association between arsenic and diabetes in populations with high exposure levels, namely, regions in Taiwan and Bangladesh with historical problems with arsenic contamination of drinking water (Figure 2). Although most members of the group considered the evidence sufficient for an association, additional research is needed to determine whether the relationship is causal. Workshop participants concluded that current evidence was insufficient for an association with diabetes and arsenic in lower--exposure areas (< 150 ppb in drinking water), such as the United States and Mexico, although recent studies with better measures of exposure and outcome provided increased evidence for an association (Coronado-Gonzalez et al. 2007; Del Razo et al. 2011; Ettinger 2009).

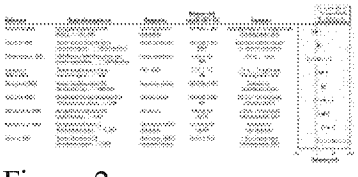

Figure 2
Association between arsenic and diabetes in areas of relatively high exposures (> 150 ppm drinking water). Studies are sorted by quality of the diagnostic from worse to better. Abbreviations: adj PR, adjusted prevalence ratio; As, arsenic; avg., **...**

The literature on arsenic and diabetes in experimental animals was judged inconclusive. The body of existing studies is highly diverse, with considerable variation in the duration of treatment (1 day to 2 years), routes of adminis-tration, and dose levels used in the studies. Most of the studies treated animals with sodium arsenite [As(III); arsenic tri-oxide], but other arsenicals have also been studied (Aguilar et al. 1997; Arnold et al. 2003; Hill et al. 2009; Paul et al. 2008). The studies also vary in experimental design and model systems used to assess end points relevant to diabetes as a health effect. Most of the studies were not designed to examine the diabeto-genic effects of chronic arsenic exposure. Although the literature as a whole was judged inconclusive, findings from recent studies that were designed to focus more specifically on glucose homeostasis appear consistent with those human studies that link arsenic exposure to diabetes. Supportive findings include impaired glucose tolerance in studies of mice or rats treated with As(III) for several months at drinking water concentrations from 5 to 50 ppm (Cobo and Castineira 1997; Paul et al. 2007, 2008; Wang et al. 2009). In addition, measures of insulin regulation [e.g., homeo-static model assessment (HOMA) insulin resistance)] were affected in Wistar rats treated with 3.4 mg/kg body weight/day As(III) by oral gavage for 90 days (Izquierdo-Vega et al. 2006) and in pregnant female LM/Bc/Fnn mice treated with 9.6 mg/kg As(V) by intra-peritoneal injection on gestational days 7.5 and 8.5 (Hill et al. 2009).

Most *in vitro* or mechanistic studies were not designed specifically to study the diabetogenic or adipogenic effects of arsenic. Nevertheless, these studies suggest several pathways by which

arsenic could influence pancreatic β-cell function and insulin sensitivity, including oxidative stress and effects on glucose uptake and transport, gluconeogenesis, adipocyte differentiation, and Ca^{2+} signaling (reviewed by Diaz-Villasenor et al. 2007, 2008; Druwe and Vaillancourt 2010; Tseng 2004). Studies suggest that arsenic may exert adverse effects on β-cell function *in vitro* through several mechanisms, depending on the concentration tested (Fu et al. 2010).

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http://www.niehs.nih.gov/research/supported/sep/2010/mortality/index.cfm

Arsenic-Related Mortality in Bangladesh

Joseph Graziano, Ph.D., Alexander van Geen, Ph.D. and Hanibul Ahsan, M.D., MMedSc.,
Columbia University
NIEHS Grants P30ES009089 and P42ES010349

NIEHS-supported researchers report that 21.4 percent of all deaths in the Araihazar region of Bangladesh can be attributed to well-water arsenic concentrations greater than 10 micrograms per liter. Their findings are from the first prospective study to investigate the link between arsenic exposure and mortality and are published online in Lancet.

Current estimates suggest that 35-77 million of the 125 million inhabitants of Bangladesh drink arsenic-contaminated water. More than 55 percent of the 11,746 study participants drink water with more than 50 micrograms of arsenic per liter, the current Bangladesh standard, and 75 percent consume water which is more contaminated than the World Health Organization standard of 10 micrograms per liter. However, a unique feature of this study is that it includes participants at both the low and high ends of the dose-response curve. For people exposed to the highest doses of arsenic, all-cause mortality was nearly 70 percent higher relative to those exposed to less than 10 micrograms per liter.

Arsenic-contaminated drinking water is an environmental health problem in many parts of the world including some areas of the United States. The investigators plan follow-up studies to assess other long-term effects of arsenic exposure and how they might be ameliorated by changes in exposure. However, they point out that "solutions and resources are urgently needed to mitigate the resulting health effects of arsenic exposure."

Citation: Arsenic exposure from drinking water, and all-cause and chronic-disease mortalities in Bangladesh (HEALS): a prospective cohort study. Argos M, Kalra T, Tathouz PJ, Chen Y, Pierce B, Parvez F, Islam T, Ahmed A, Rakibus-Zaman M, Hasan R, Sarwar G, Slakovich V, van Geen A, Graziano J, Ahsan H. Lancet. 2010 Jun 19: DOI:10.1016/S0140-673(10)60481-3.

Arsenic Exposure may Increase Mortality from Tuberculosis

Allan H. Smith, M.D., Ph.D.
University of California Berkeley
NIEHS Grants P42ES004705 and R01ES010033

Citation: Smith AH, Marshall G, Yuan Y, Liaw J, Ferreccio C, Steinmaus C. Evidence from Chile that arsenic in drinking water may increase mortality from pulmonary tuberculosis. Am J Epidemiol. 2011 Feb 15;173(4):414-20.

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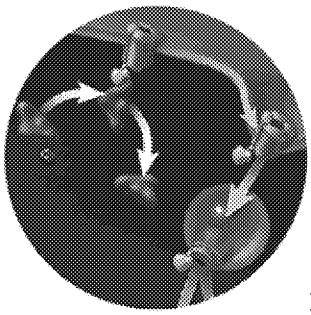
http://www.dartmouth.edu/~toxmetal/research-projects/arsenic-innate-immunity.html

Arsenic and Innate Immune Function of the Lung



Project Leader:

Bruce A. Stanton, Ph.D.
Director, Toxic Metals
Superfund Research Program
Professor, Department of Microbiology and Immunology
Andrew C. Vail Professor
Geisel School of Medicine at Dartmouth

Chronic exposure to arsenic in the drinking water is a worldwide health concern and is associated with an increased risk of lung disease including bacterial infections. Recent studies have demonstrated that arsenic regulates the expression of a number of genes involved in the innate immune response in the lung, and thereby the ability to eliminate bacterial infections.
http://www.niehs.nih.gov/research/supported/sep/2004/iqfunctn/index.cfm

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Water Arsenic Exposure in Bangladesh Reduces Children's Intellectual Function

Joseph H. Graziano, Ph.D.
Mailman School of Public Health, Columbia University
P30ES09089 and P42ES10349

Implications: These findings of a strong association between arsenic exposure and intelligence deficits in children add to the tragedy occurring from arsenic exposure in Bangladesh and in other parts of the world. They point out the dire need to find an effective remediation strategy to

prevent arsenic exposure in parts of the world where it is endemic. The authors note that, "The global community has been slow in responding to the public health significance of arsenic exposure in Bangladesh, despite the enormous scope of the problem." They hope "... the present findings add a new sense of urgency to efforts aimed at alleviating and eliminating" arsenic exposure in Bangladesh.

Citation: Wasserman GA, Liu X, Parvez F, Ahsan H, Factor-Litvak P, van Geen A, Slavkovich V, LoIacono NJ, Cheng Z, Hussain I, Momotaj H, Graziano JH. Water arsenic exposure and children's intellectual function in Araihazar, Bangladesh. Environ Health Perspect. 2004 Sep;112(13):1329-33.

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http://www.niehs.nih.gov/research/supported/sep/2007/newborns/index.cfm

Prenatal Arsenic Exposure Detected in Newborns

Leona Samson, Ph.D. and Rebecca Fry, Ph.D.
Massachusetts Institute of Technology
NIEHS Grants R01ES011399 ∧ P30ES002109

MIT researchers have found that the children of mothers whose water supplies were contaminated with arsenic during their pregnancies harbored gene expression changes that may lead to cancer and other diseases later in life. In addition to establishing the potentially harmful effects of these prenatal exposures, the new study also provides a possible method for screening populations to detect signs of arsenic contamination.

The evidence comes from a genetic epidemiologic study including 32 mothers and their children in a province of Thailand with heavy arsenic water contamination caused by tin mining. The mean arsenic level in the water was 503.5 micrograms/liter or about 50 times higher than current U.S. standards. Similar water levels of arsenic are also found in many other regions, including the U.S. Southwest.

The scientists identified 11 gene transcripts that predicted with about 80% accuracy whether the infant had been exposed to arsenic. Eight of the 11 genes were involved in inflammatory processes. **This is the first time evidence of such genome-wide changes resulting from prenatal exposure has ever been documented from any environmental contaminant. It suggests that even when water supplies are cleaned up and the children never experience any direct exposure to the pollutant, they may suffer lasting damage.**

Citation: Fry RC, Navasumrit P, Valiathan C, Svensson JP, Hogan BJ, Luo M, Bhattacharya S, Kandjanapa K, Soontararuks S, Nookabkaew S, Mahidol C, Ruchirawat M, Samson LD. Activation of Inflammation/NF-kappaB Signaling in Infants Born to Arsenic-Exposed Mothers. PLoS Genet. 2007 Nov 23;3(11).

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http://www.niehs.nih.gov/news/newsroom/releases/2012/april04/index.cfm

4 Apr 2012: Arsenic turns stem cells cancerous, spurring tumor growth

Researchers at the National Institutes of Health have discovered how exposure to arsenic can turn normal stem cells into cancer stem cells and spur tumor growth. Inorganic arsenic, which affects the drinking water of millions of people worldwide, has been previously shown to be a human carcinogen. A growing body of evidence suggests that cancer is a stem-cell based disease. Normal stem cells are essential to normal tissue regeneration, and to the stability of organisms and processes. But cancer stem cells are thought to be the driving force for the formation, growth, and spread of tumors.

Michael Waalkes, Ph.D., and his team at the National Toxicology Program Laboratory, National Institute of Environmental Health Sciences, part of NIH, had shown previously that normal cells become cancerous when they are treated with inorganic arsenic. This new study shows that when these cancer cells are placed near, but not in contact with normal stem cells, the normal stem cells very rapidly acquire the characteristics of cancer stem cells. It demonstrates that malignant cells are able to send molecular signals through a semi-permeable membrane, where cells can't normally pass, and turn the normal stem cells into cancer stem cells.

"This paper shows a different and unique way that cancers can expand by recruiting nearby normal stem cells and creating an overabundance of cancer stem cells," said Waalkes. "The recruitment of normal stem cells into cancer stem cells could have broad implications for the carcinogenic process in general, including tumor growth and metastases."

This reveals a potentially important aspect of arsenic carcinogenesis and may help explain observances by researchers working with arsenic that arsenic often causes multiple tumors of many types to form on the skin or inside the body. The paper is online in Environmental Health Perspectives.

Waalkes' lab started working with stem cells about five years ago. The researchers used a prostate stem cell line, not embryonic stem cells.

"Using stem cells to answer questions about disease is an important new growing area of research. Stem cells help to explain a lot about carcinogenesis, and it is highly likely that stem cells are contributing factors to other chronic diseases," Waalkes said.

Stem cells are unique in the body. They stay around for a long time and are capable of dividing and renewing themselves. "Most cancers take 30 or 40 years to develop," said Linda Birnbaum, Ph.D., director of NIEHS and NTP. "It makes sense that stem cells may play a role in the developmental basis of adult disease. We know that exposures to toxicants during development and growth can lead to diseases later in life."

Next, the laboratory team will look to see if this finding is unique to arsenic or if it is applicable to other organic and inorganic carcinogens.

Reference: Xu Y, Tokar EJ, Sun Y, Waalkes MP. 2012. Arsenic-transformed malignant prostate epithelia can convert non-contiguous normal stem cells into an oncogenic phenotype. Environ Health Perspect; doi:10.1289/ehp.1204987 [online 2012 April].